JournalScan

Alistair Lindsay, Editor

Please visit the Heart website (www.heartjnl.com) for links to these articles – many to full text.

GENERAL CARDIOLOGY

Meta-analysis shows no clear benefit from folate supplementation ► Although several epidemiological studies have suggested that folate supplements can decrease the risk of cardiovascular disease, the results of clinical trials to date have been mixed. To investigate this further, Bazzano and colleagues performed a meta-analysis of all folate supplementation trials performed over the past 40 years that were found on a MEDLINE search. From 165 relevant reports, only 12 randomised controlled trials compared folate supplementation with placebo or usual care and used clinical cardiovascular disease as an end point; in total these trials analysed 16 958 participants. The overall relative risks of cardiovascular outcomes for patients treated with folate supplementation were 0.95 (CI 0.88 to 1.03) for cardiovascular disease overall, 1.04 (0.92 to 1.17) for coronary heart disease, 0.86 (0.71 to 1.04) for stroke and 0.96 (0.88 to 1.04) for all-cause mortality. The relative risk was consistent among patients with pre-existing renal or cardiovascular disease. Thus, no overall net benefit of folate supplementation on cardiovascular disease or all-cause mortality was shown. Several ongoing trials with large sample sizes may provide a definitive answer to this question.

▲ Bazzano LA, Reynolds K, Holder KN, *et al*. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *JAMA* 2006;**296**:2720–6.

Bupropion safe and effective for smoking cessation following acute coronary syndromes ► Cardiovascular mortality following myocardial infarction (MI) can be reduced by cessation of smoking. Bupropion is effective for smoking cessation, but its safety and efficacy in hospitalised smokers with acute cardiovascular disease has not previously been studied. A total of 248 smokers admitted with acute coronary syndromes were randomised to 12 weeks of sustained-release bupropion (300 mg) or placebo. In addition, all subjects had smoking-cessation counselling in the hospital and for 12 weeks after discharge. Follow-up of tobacco abstinence, cardiovascular mortality and new cardiovascular events was made at 3 months and 1 year. Validated tobacco abstinence rates in bupropion and placebo groups were 37.1% vs 26.8% (odds ratio (OR) 1.61; p = 0.08) at 3 months and 25.0% vs 21.3% (OR 1.23; p = 0.49) at 1 year. The adjusted odds ratio, after controlling for number of cigarettes per day, depression symptoms, prior bupropion use, hypertension and length of stay, was 1.91 (95% CI 1.06 to 3.40; p = 0.03) at 3 months and 1.51 (95% CI 0.81 to 2.83) at 1 year. Bupropion and placebo groups did not differ in cardiovascular mortality at 1 year (0% vs 2%), in blood pressure at follow-up, or in cardiovascular events at end-of-treatment (16% vs 14%) or at 1 year (26% vs 18%). Therefore, overall Bupropion marginally improved short-term but not long-term smoking cessation rates when compared with intensive counselling, but seemed to be safe in patients admitted with acute coronary syndromes.

▲ Rigotti NA, Thorndike AN, Regan S, *et al*. Bupropion for smokers hospitalised with acute cardiovascular disease. *Am J Med* 2006;**119**:1080–7.

Improving compliance with a comprehensive pharmacy care programme ► Non-compliance with a prescribed drug diminishes potential health benefits. Particularly, the elderly, who are often on multiple drugs, and at an increased risk of non-compliance. A comprehensive pharmacy care programme, including standardised drug education, regular follow-up by pharmacists and drugs dispensed in time-specific packs, could help to overcome this problem. This trial used such measures and investigated whether effects on blood pressure (BP) and low-density lipoprotein cholesterol could be noted. A total of 200 elderly patients (77.1% men, mean age 78 years) taking a mean of nine drugs for chronic diseases were enrolled over a 2-year period. After 6 months of intervention, drug adherence was 96.9% and was associated with significant improvements in systolic BP and low-density lipoprotein cholesterol. At 6 months after randomisation, the persistence of drug adherence decreased to 69.1% among those patients assigned to usual care, whereas it was sustained at 95.5% in the interventional group. A pharmacy care programme can therefore lead to increases in drug adherence, drug persistence and clinically meaningful reductions in BP, whereas discontinuation of the programme was associated with decreased drug adherence and persistence in this study.

▲ Jeannie K Lee, Karen A Grace, Allen J Taylor. Effect of a pharmacy care program on medication adherence and persistence, blood pressure and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA* 2006;**296**:2563–71.

Can statins prevent perioperative coronary events? ► The non-lipid-lowering effects of statins, such as plaque stabilisation and anti-inflammatory modulation, are hypothesised to help prevent perioperative MI. Two reviewers independently extracted data from studies that reported on acute coronary syndromes and/or mortality in patients receiving versus those not receiving statins during the perioperative period. Overall, 18 studies were identified: 2 randomised trials (n = 177), 15 cohort studies (n = 799 632) and 1 case–control study (n = 480); 12 studies enrolled patients undergoing non-cardiac vascular surgery, 4 enrolled patients undergoing coronary artery bypass surgery and 2 enrolled patients undergoing various surgical procedures. In the randomised trials, the summary OR for death or an acute coronary syndrome during the perioperative period with statin use was 0.26 (95% CI 0.07 to 0.99), whereas the summary OR in the cohort studies was 0.70 (0.57 to 0.87). Thus, although the pooled cohort data suggest a statistically significant result in favour of statin use, the authors note that statins were not randomly allocated, results in the retrospective studies were larger than those in the prospective cohort, and dose, duration and safety of statin use was not reported. Further clinical trials are needed before the routine administration of statins to reduce perioperative cardiovascular risk can be recommended. It is not yet time for statins to be the universal panacea.

▲ Kapoor AS, Kanji H, Buckingham J, *et al*. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. *BMJ* 2006;**333**:1149.

Decreased cardiac function more prevalent in obstructive sleep apnoea ► An observational study of 86 patients diagnosed with obstructive sleep apnoea (OSA) was conducted to investigate cardiac performance in this group of patients. Stroke volume and cardiac output were measured using impedance cardiography and corrected for body surface area to give a Stroke Index and Cardiac Index. Daytime sleepiness was also quantified using the Epworth Sleepiness Scale, and a higher score (indicating more daytime sleepiness) was significantly related to lower Stroke Index and Cardiac Index. In multiple regression analyses, the relationships of Epworth Sleepiness Scale Score with both Stroke Index and Cardiac Index were significant ($p<0.05$), even after controlling for age, sex, ethnicity, respiratory disturbance index and mean sleep oxygen saturation.

Cardiac output is thus decreased in patients with OSA and is independently associated with daytime sleepiness. Although not new data, they illustrate the cardiac risk faced by these patients and that relieving the OSA improves cardiac function.

▲ Choi J-B, Nelesen R, Loredo JS, *et al*. Sleepiness in obstructive sleep apnea: a harbinger of impaired cardiac function? *Sleep* 2006;**29**:1531–6.

Cyclo-oxygenase 2 and non-steroidal anti-inflammatory drugs show similar rates of cardiovascular events ► The Multinational Etoricoxib and Diclofenac Arthritis Long-term trial was designed to precisely compare the risk of thrombotic cardiovascular

events in patients taking the cyclo-oxygenase 2 (COX-2)-selective inhibitor, etoricoxib, with patients using the more traditional non-steroidal anti-inflammatory drug (NSAID), diclofenac. Patients with osteoarthritis or rheumatoid arthritis were randomly assigned to etoricoxib (60 or 90 mg daily) or diclofenac (150 mg daily). Overall, 34 701 patients were enrolled, and the average duration of treatment was 18 months. In all, 320 patients in the etoricoxib and 323 in the diclofenac group had thrombotic cardiovascular events, yielding event rates of 1.24 and 1.30 per 100 patient-years and a hazard ratio (HR) of 0.95 for etoricoxib compared with diclofenac. Rates of upper gastrointestinal clinical events (which included perforation, obstruction, bleeding and ulcer) were lower with etoricoxib than diclofenac (0.67 vs 0.97/100 patient-years; HR 0.69), but the rates of complicated upper gastrointestinal events were similar for etoricoxib (0.30) and diclofenac (0.32). Therefore, in this analysis thrombotic cardiovascular events were similar between the COX-2-selective inhibitor, etoricoxib, and the (NSAID) diclofenac. The results of subgroup analyses suggested that cardiovascular risk factors and low-dose aspirin use did not affect the absence of difference noted. However, the authors do highlight that in clinical practice, the choice of anti-inflammatory agent needs to take into consideration several other clinical factors—for example, the use of etoricoxib was associated with higher rates of congestive heart failure and discontinuation due to hypertension.

▲ Cannon CP, Curtis SP, FitzGerald GA, *et al*. MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;**368**:1771–81.

Biomarkers and prediction of cardiovascular risk ► Traditional risk factors such as dyslipidaemia, smoking, hypertension and diabetes do not fully explain cardiovascular risk. Simultaneous measurement of several novel markers could potentially improve the risk-stratification process, the so-called ''multimarker approach''. Ten biomarkers (C reactive protein, B-type natriuretic peptide, N-terminal proatrial natriuretic peptide, aldosterone, renin, fibrinogen, D dimer, plasminogen activator inhibitor type 1, homocysteine and urinary albumin-to-creatinine ratio) were measured in 3209 participants attending a routine examination cycle of the Framingham Heart Study, who were then followed up for a median of 7.4 years. Two hundred and seven participants died and 169 had a first major cardiovascular event. The most informative biomarkers for predicting cardiovascular events were B-type natriuretic peptide and urinary albumin-to-creatinine ratio. Individuals with ''multimarker scores'' in the highest quintile, compared with those with scores in the lowest two quintiles, had elevated risks of death (adjusted HR 4.08, p=0.001) and major cardiovascular events (adjusted HR 1.84, p=0.02). However, the addition of multimarker scores to conventional risk factors resulted in only a small increase in the ability to classify risk. Assessment of novel biomarkers may still be useful for identifying high-risk subgroups but the future success of this strategy rests in identifying new markers, and also in the development of simple and inexpensive screening tests. If additional value is only marginal, and there are no easy cut-off levels to rule-in or rule-out risk, then they remain a research tool.

▲ Wang TJ, Gona P, Larson MG, *et al*. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;**355**:2631–9.

INTERVENTIONAL CARDIOLOGY

Meta-analysis indicates higher late thrombotic risk with drug-eluting stents ► How common is late thrombosis of drug-eluting stents (DES)? To attempt to answer this question, Bhatt and colleagues from the Cleveland Clinic performed a meta-analysis of 14 contemporary trials comparing 6675 patients with paclitaxel or sirolimus DES. Eight of the trials had >1 year of clinical follow-up. The incidence of very late thrombosis (>1 year after the index event) was 5.0 events per 1000 patients with DES, whereas no events were seen in patients with bare-metal stent (BMS; risk ratio (RR) 5.02; p=0.02). Among sirolimus trials, the incidence of late stent thrombosis was 3.6 per 1000 patients with a sirolimus-eluting stent, with a median time to thrombosis of 15.5 months. Among patients with paclitaxel-eluting stents, the incidence of very late thrombosis was 5.9 per 1000 patients, with a median time to thrombosis of 18 months. Thus, although the overall incidence is low, DES show an increased incidence of late stent thrombosis when compared with BMS. In this trial, more risk was seen with paclitaxel stents, although it remains quite possible that sirolimus stents similarly increase the risk of late stent thrombosis. A new term that is now in the literature is the ''Dublin Criteria'', to adjudicate definite, probable and possible stent thrombosis. When looking at further data, definite and probable stent thrombosis events need to be assessed, along with an assessment of the risk of restenosis (which can also present as an acute coronary syndrome).

▲ Bavry AA, Kumbhani DJ, Helton TJ, *et al*. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;**119**:1056–61.

Long-term clopidogrel use associated with better outcomes ► Premature discontinuation of antiplatelet treatment has been associated with stent thrombosis in DES, so what is the minimum necessary duration of aspirin and clopidogrel treatment after DES implantation? An observational study from the Duke Heart Center (Durham, North Carolina, USA) looked at 4666 patients undergoing percutaneous coronary intervention (PCI) with either a BMS (n=3165) or DES (n=1501) over a 6-year period. Patients who were event-free at 6 and 12 months were then studied in one of the four groups: DES with clopidogrel; DES without clopidogrel; BMS with clopidogrel and BMS without clopidogrel. The main outcome measures were death, non-fatal MI and the composite of death or MI at 24-month follow-up. Among patients with DES who were event-free at 6 months (637 with and 579 without clopidogrel), clopidogrel use was a significant predictor of lower adjusted rates of death (2.0% with vs 5.3% without; p=0.03) and death or MI (3.1% vs 7.2%; p=0.02) at 24 months. Among patients with BMS (417 with and 1976 without clopidogrel), there were no differences in death, or death and MI combined. Among patients with DES who were event-free at 12 months (252 with and 276 without clopidogrel), clopidogrel use continued to predict lower rates of death (0% vs 3.5%; p=0.004) and death or MI (0% vs 4.5%; p<0.001) at 24 months; whereas in patients with BMS, clopidogrel use again made no differences to these outcomes. Thus these data suggest that the extended use of clopidogrel in patients with DES may be associated with a reduced risk of death or MI. The authors suggest a large-scale randomised clinical trial to further investigate the appropriate duration of clopidogrel treatment.

▲ Eisenstein EL, Anstrom KJ, Kong DF, *et al*. Clopidogrel use and long-term clinical outcome after DES implantation. *JAMA* 2007;**297**:159–68.

Improving door-to-balloon times in primary percutaneous coronary intervention ► What factors influence door-to-balloon time when performing primary percutaneous coronary intervention? To identify strategies associated with shorter treatment times, 365 hospitals were surveyed with a questionnaire that included 32 closed-end items identifying 28 key hospital strategies that influence the care of patients with acute MI undergoing primary PCI. In multivariate analysis, six strategies were significantly associated with a faster door-to-balloon time. These included having emergency medicine doctors activate the catheterisation laboratory (mean reduction in door-to balloon time 8.2 min), having a single call to a central page operator activate the laboratory (13.8 min), having the emergency department activate the catheterisation laboratory while the patient is enroute to the hospital (15.4 min), expecting staff to arrive in the catheterisation laboratory within 20 min after being paged (19.3 min), having a senior cardiologist always on site (14.6 min) and having real-time (within 1 week) feedback to staff in the emergency department and catheterisation laboratory of door-to-balloon times (8.6 min). There is clearly a balance to be achieved between optimal response times and higher costs and possible staff dissatisfaction. All these strategies are being studied in busier units in the UK, at present, in the National Infract Angioplasty Project. The only question to pose is whether hospitals doing <60 PCIs per year (two-thirds of the cohort studied in the *N Engl J Med* paper) should be doing primary PCI at all.

▲ Bradley EH, Herrin J, Wang Y, *et al*. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med* 2006;**355**:2308–20.

▲ Moscucci M, Eagle KA. Reducing the door-to balloon time for myocardial infarction with ST-segment elevation. *N Engl J Med* 2006;**355**:2364–5.

BASIC SCIENCE

C reactive protein polymorphisms linked to cardiovascular risk ► C reactive protein (CRP) has been implicated both as a marker

and as playing a direct role in the pathogenesis of cardiovascular disease. To assess whether polymorphisms in the CRP gene are clinically significant, four polymorphisms were genotyped in 3941 white and five polymorphisms in 700 African–American patients without cardiovascular disease (MI or stroke) at study entry. Patients were then followed up for a median of 13 years; the main outcome measures included the relationships between CRP polymorphisms and baseline carotid intima-media thickness, occurrence of MI and stroke, and cardiovascular disease mortality during follow-up. Two alleles (1919T and 790T) were associated with higher CRP levels in white and black participants, respectively; another (3872A) was associated with lower CRP levels in white and black participants, and one allele (2667C) was associated with lower CRP levels in white participants only. No association was found between carotid intima-media thickness and any CRP gene polymorphism in either population. In white participants, the 1919T allele was associated with increased risk of stroke for TT vs AA (HR 1.4) and for cardiovascular disease mortality (HR 1.40). In black participants, homozygosity for the 790T allele was associated with a fourfold increased risk of MI compared with homozygosity for the 790A allele. The minor alleles of the two polymorphisms associated with lower plasma CRP concentration in white participants (2667C and 3872A) were associated with the decreased risk of mortality from cardiovascular disease. This study shows that genetic polymorphisms in the CRP gene are associated with high and low CRP levels, with particular genotypes being associated with event risks independent of the initial baseline CRP level.

▲ Leslie A Lange, Christopher S Carlson, Lucia A Hindorff, *et al*. Association of Polymorphisms in the *CRP* gene with circulating C-reactive protein levels and cardiovascular events. *JAMA* 2006;**296**:2703–11.

Journals scanned

American Journal of Medicine; American Journal of Physiology: Heart and Circulatory Physiology; Annals of Emergency Medicine; Annals of Thoracic Surgery; Archives of Internal Medicine; BMJ; Chest; European Journal of Cardiothoracic Surgery; Lancet; JAMA; Journal of Clinical Investigation; Journal of Diabetes and its Complications; Journal of Immunology; Journal of Thoracic and Cardiovascular Surgery; Nature Medicine; New England Journal of Medicine; Pharmacoeconomics; Thorax

Reviewers

Dr Alistair Lindsay, Dr Katie Qureshi

IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2006.094227

Split coronary artery seen with computed tomography and magnetic resonance imaging

A 62-year-old man with onset of atypical angina pectoris was referred to our institution to rule out coronary artery disease. He had no cardiovascular risk factors other than smoking and arterial hypertension. Electrocardiogram and stress electrocardiogram were both negative. We performed non-invasive coronary angiography using both multislice computed tomography and magnetic resonance imaging. Neither examination showed any major coronary stenoses in the left coronary artery system, but a split origin of this coronary artery (fig 1A, B). Both the left anterior descending artery and the left circumflex artery originated from separate but adjacent ostia in the left sinus of Valsalva. This anomaly is the most common coronary artery anomaly, with a prevalence of approximately 0.4%, which causes no haemodynamic impairment and thus, should be considered benign. The absence of major stenoses and the presence of a split left coronary artery were confirmed on conventional coronary angiography, with injections of selective contrast agents into the left anterior descending artery (fig 1C) and the left circumflex artery (fig 1D). Both multislice computed tomography and magnetic resonance imaging have recently been shown to allow non-invasive detection of coronary anomalies. As these images show, both non-invasive methods are of clinical value for assessing proximal coronary anomalies.

M Dewey, F Teige, K Stangl
marc.dewey@charite.de